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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/516,310	LIN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,9-26 and 33* is/are pending in the application.

4a) Of the above claim(s) *16-26 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 June 2004 has been entered.

Claims 16-26 and 33 were withdrawn from consideration and claims 6-15 and 34-38 were considered in the Final Office Action mailed 24 February 2003. Claims 7, 8 and 34-38 were canceled and claims 6, 11 and 23 were amended in the 21 June Paper. Claims 6, 9-26 and 33 are pending and claims 6 and 9-15 are presently under consideration.

Response to Amendment

Rejection of claims 7, 8 and 34-38 is rendered moot by cancellation thereof.

Claims 6 and 9-15 stand rejected under 35 USC 112, first paragraph, for lack of enablement for reasons of record and herein below in the response to arguments.

Claims 6, 10, 11 and 13-15 stand rejected under 35 USC 112, first paragraph for insufficient written description for reasons of record and herein below in the response to arguments.

Rejection of claims 6-10 under 35 U.S.C. 112, first paragraph, as containing new matter is withdrawn in view of the amendments to claim 6.

Rejection of claims 6, 9 and 10 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of the amendments.

Response to Arguments

The 26 January Request for Continued Examination requests consideration of the amendments/reply under 37 CFR §116 previously filed on 25 August 2003. A complete reply to the arguments filed with the 25 August submission was contained in the Advisory Action mailed 30 September 2003. Those arguments are reiterated and expanded to include findings from the updated search herein below.

Declaration under 37 CFR 1.132

The declaration under 37 CFR 1.132 filed 27 August 2003 is insufficient to overcome the rejection of claims 6 and 9-15 based upon insufficiency of the disclosure under 35 U.S.C. §112, first paragraph, as set forth in the Final Office Action because they do not support enablement for the full scope of the claims.

The showings of the declaration provide evidence that a K-FGF signal peptide fused to a nuclear localization signal from NG-κB, when administered to a mouse model of septic shock, attenuated systemic inflammation and tissue injury. Based on the findings presented, Applicant concludes that the fusion protein is systemically absorbed and crosses the plasma membrane, and

importation-competent signal peptides are an effective means for transporting biologically active molecules into cells in a subject. Although these showings might be enabling for a method of treating sepsis comprising administering an SN50 peptide fused to the signal peptide of K-FGF, they do not provide enablement for the broad scope of the claims for reasons of record and herein below. Furthermore, as the instant specification fails to contemplated critical elements of the method reduced to practice in the declaration, such as the specific patient population and effective dosage and route of administration, the disclosure would not enable the skilled artisan to practice a method of treating sepsis as demonstrated in the declaration.

The showings of the declaration have been fully considered; however, based on the record as a whole, the evidence is deemed insufficient to overcome the outstanding rejection of claims 6 and 9-15.

Rejections under 35 U.S.C. §112, first paragraph, (enablement):

Applicant's arguments regarding enablement of the claims are first directed to the Examiner's statements regarding targeting of the biologically active molecule. Applicant argues that, contrary to the Examiner's assertion, avoiding systemic importation into all cells is not critical to the invention. Applicant cites teachings from the specification which indicate that targeting of the biologically active molecule might be achieved by various means and does not require some means to prevent importation of the molecule into all cells. This argument has been fully considered but is not found persuasive because the claims clearly encompass delivery of biologically active molecules such as toxin polypeptides, which the skilled artisan would expect to require targeting to have therapeutic utility. The Examiner acknowledges that some

embodiments of the claimed invention would not require targeting selected cells for therapeutic effect, as demonstrated by the showings in the Declaration of Dr. Hawiger. However, given that the claims are directed to methods of using widely divergent biologically active molecules, including molecules that would require targeting to selected cells to be used therapeutically, the showings of the Declaration do not support enablement for the full scope of the claimed subject matter.

Furthermore, almost 10 years after the effective filing date of the instant application, the art recognized the lack targeting as an important unanswered question and possible limitation to the use of translocating peptides *in vivo*. Kabouridis (2003) *TRENDS Biotechnol.* 21:498-503 teaches, "a major disadvantage [of using translocating peptides] is lack of targeting specificity. Therefore, for each case, it will be important to establish not only that the PTD-chimera has beneficial effect on diseased cells but also that it ahs no adverse effects on healthy tissue" (first full paragraph on page 502). Schwarze *et al.* (2000) *Trends Cell Biol.* 10:290-295 concurs with the teachings of Kabouridis, stating, "[a]n effective drug must be active only in the diseased cell. As translocating proteins can readily enter all cell types, specificity must be built into the molecule" (second full paragraph on page 294). Thus, Kabouridis and Schwarze *et al.* clearly teach that the usefulness of any given method of delivering a peptide, polypeptide or protein into a cell in a subject will have to be determined on a case by case basis by empirical experimentation, at least because the effects of an untargeted peptide, polypeptide or protein on the organism as a whole is unpredictable.

Kabouridis goes on to teach additional possible obstacles to using translocating peptides *in vivo* including immunogenicity of the translocating peptide itself or its cargo, which also

contribute to the unpredictability of the present method (second full paragraph on page 294). Schwarze *et al.* goes on to teach that basic pharmacological questions of tissue distribution, protein half-life, immunogenicity and modes of delivery are also important questions that need to be addressed in a quantitative fashion (paragraph bridging pages 294-295). Thus, the teachings of Kabouridis and Schwarze *et al.* indicate that, even years after the effective filing date of the instant application, many basic questions regarding the effective use of translocating peptides *in vivo* remained to be answered. As the instant specification provides no guidance directed to this art-recognized unpredictability, these basic questions will have to be answered through experimentation before the broad scope of the instant claims is enabled.

Another aspect of the claimed method which must be addressed on a case-by-case basis is the operability of the cargo delivered by importation competent signal peptide. The specification teaches, "[n]aturally, only those molecules which hare of a size which can be imported into the cell are within the scope of the invention. However, since very large proteins (ranging form molecular weights of about 100,000 to around 1 million) are exported by cells (*e.g.*, antibodies, fibrinogen, and macroglobulin), very large proteins can be imported into cells by this method" (page 6). However, the accuracy of this assumption clearly requires that the mechanism by which these large proteins are exported is the same as the mechanism by which hydrophobic importation competent signal peptides import proteins. Most large proteins are secreted by vesicular transport from the endoplasmic reticulum via the Golgi to the cell surface and fusion of the secretory vesicles with the plasma membrane. In contrast, in an article published recently, applicant presents data indicating that the hydrophobic importation polypeptides of the instant claims ferry their cargo through the plasma membrane directly, absent endocytosis (see Veach *et*

al. (2004) *J. Biol. Chem.*279:11425-11431, throughout, especially Figure 5 and the caption thereto). In the first paragraph after the abstract, Applicant acknowledges, "[t]he plasma membrane imposes tight control on the access of extracellular peptides and proteins to the cell interior." Thus, absent evidence to the contrary, one of ordinary skill in the art would not expect the ability of hydrophobic importation polypeptide fusion protein to cross the plasma membrane to be independent of the cargo peptide, polypeptide or protein comprised within the fusion protein. Lindgren *et al.* (2000) *Trends Pharmacol. Sci.* 21:99-103, reviewing the available literature regarding cell-penetrating peptides, cites only one example of a large protein being transported by a signal-sequence-based peptide, *i.e.*, glutathione-*S*-transferase (GST; see especially Table 1 and the caption thereto). However, it was recently demonstrated by Namiki *et al.* (2003) *Biochem. Biophys. Res. Commun.* 305:592-597, that the translocation of GST is independent of the signal-sequence-based peptide (see especially the abstract). Thus, the teachings from the art and specification clearly to not provide sufficient guidance with regard to which cargo proteins, peptides or polypeptides can be delivered into a cell *in vivo* such that the skilled artisan could practice the broad claims without undue experimentation.

In response to the Examiner's assertion that undue experimentation would be required to practice the method using the broad scope encompassed by the importation competent signal peptide of the claims, Applicant cites a general teaching from the specification indicating that the importation competent signal peptide is about 10-50 amino acid residues and contains a hydrophobic, lipid-soluble portion (typically about 55-60% hydrophobic residues). Applicant argues that, in view of these teachings and teachings from the art as to how one could assay for the activity of an importation competent signal peptide, the experimentation required to practice

the invention using the full scope of importation signal peptides would be routine. This argument is not persuasive because it fails to take into account the tremendous number of peptides that would have to be assayed for activity. Even if the structural features set forth in the specification were taken as absolute limitations on the importation competent signal peptide of the claims (in fact, they are only suggested as possibly relevant features) the limitations would be common to millions of peptides, only a small fraction of which would have the activity of an importation signal peptide. With regard to claims that comprise broad generic limitations, the standard for enablement is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414; hereinafter *Atlas*). Further, *Atlas* provides, "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid" (page 414). Applicant's arguments fail to take into account the enormous scope of the importation competent signal peptide of the claims. Because determining which embodiments that were conceived, but not yet made, would be inoperative or operative would clearly require expenditure of more effort than is normally required in the art, practicing the full scope of the claimed method would require undue experimentation.

Applicant's arguments have been fully considered but are not deemed persuasive either individually or viewed as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure.

Rejections under 35 U.S.C. §112, first paragraph, (possession):

In response to the Examiner's arguments of record regarding written description for the method as it broadly encompasses using any importation signal peptide, Applicant asserts that: (1) the specification indeed provides an adequate written description of the importation competent signal peptides to be used in the claimed method, (2) notwithstanding this, the specification need not provide a written description of the importation peptides to be used in the claimed method because it is only the claimed method itself that must be described, and (3) the specification need not provide a written description of the importation competent signal peptides to be used in the claimed method because the peptides are only involved in making and using the claimed method and are not the claimed method itself.

To support the first assertion, Applicant particularly cites the Written Description Guidelines (66 Fed. Reg. 1,099 (Jan. 5, 2001)) and Enzo Biochem. V. Gen-probe, 296 F.3d 1316, 1324 (Fed. Cir. 2002). Applicant states: "The standards embodied in the Written Description Guidelines in general, and in Example 16 of the Synopsis of Guidelines in particular, have recently been adopted by the Federal Circuit as valid for the analysis of compliance with the written description requirement...*Enzo II* states that "it is not correct...that all functional descriptions...fail to meet the written description requirement." Id. at 1324. Thus, a claim to method that includes the step of administering to the subject a complex comprising a peptide, polypeptide, or protein linked to a mammalian hydrophobic importation competent signal peptide as functionally and structurally defined by the specification (e.g., at page 10, line 20, through page 21, line 16), is adequately described even in the absence of description of the

structure-function correlation between specific amino acids and the importation function of the signal peptide, as required by the Office Action" (page 11).

These arguments have been fully considered but are not found persuasive because they mischaracterize the statements found in Enzo and the Written Description Guidelines. The statement from Enzo cited by Applicant is immediately followed by, "[i]n its Guidelines, the PTO has determined that the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*" (emphasis added in Enzo). Citing Example 16 of the Written Description Guidelines, the court adds, "the PTO would find compliance with § 112, ¶ 1, for a claim to an 'isolated antibody capable of binding to antigen X,' notwithstanding the functional definition of the antibody, *in light of 'the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature.*'" (emphasis added). Thus, the court clearly indicates that, contrary to Applicant's assertion, a recitation of functional characteristics alone does not provide adequate written description for a molecule. Instead, the statements made in Enzo and the Written Description Guidelines, when viewed in context, provide that a recitation of function must be "coupled with a known or disclosed correlation between function and structure". In contrast to the antibody of Example 16 of the Synopsis of Guidelines referred to in Enzo, the instant importation competent polypeptide does not have well defined structural characteristics and neither the art nor the specification disclose a correlation between function

and structure. This is evidenced by Applicant's own teachings in Veach *et al.* (*supra*) wherein the authors report studies aimed at analyzing the mechanism of hydrophobic importation polypeptide translocation for the stated purpose of facilitating the rational design of a new generation of cell-permeant peptides (first full paragraph on page 11426). In the publication Applicant suggests that there is a proline residue comprised within hydrophobic importation polypeptides that is critical to their ability to cross the plasma membrane (see especially the first full paragraph on page 11430 and Figure 5 and the caption thereto). However, the Examiner can find no reference to this critical proline in the instant disclosure. Thus, it would appear that the structural features disclosed in the present application do not adequately convey the necessary common attributes or features of the elements possessed by the members of the genus of a hydrophobic importation polypeptide.

Next, Applicant asserts that a claim to a method does not require description of the structure of compounds used in the method. Applicant states, "the written description of a method invention requires description only of the acts to be performed (because a method (e.g., one or more acts) is what the invention is)" (page 12). This argument has been fully considered, however it is the Examiner's position that a description of a method of using an importation competent signal peptide must describe that which is being used in the method. Applicant seems to be arguing that a method of delivering a biologically active molecule into a cell need not describe the active agent used in delivering said biologically active molecule; that a recitation of function in the context of a positive process step meets the written description requirement of 35 U.S.C. §112, first paragraph. By this reasoning, a claim to a method of curing cancer comprising administering an agent that cures cancer also meets the written description requirement.

Applicant argues that nothing in the statute or the case law requires a written description of anything other than the claimed invention for compliance with the written description requirement. While the Examiner accepts this general premise, there is nothing to suggest that a description of the materials used in a method is irrelevant to the description of the method itself. In contrast, it is the Examiner's position that claims directed to a method of delivering an agent are not adequately described if the skilled artisan could not envision what is being delivered. This is supported by the "Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, first paragraph, 'Written Description' Requirement" (*Federal Register*/ Vol. 66, No. 4/Friday, January 5, 2001/Notices), which state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

Next, Applicant argues that the requirement that the manner and process of making and using the claimed invention be described is not part of the written description requirement. Applicant discusses the case law establishing that the written description requirement of 35 U.S.C. §112, first paragraph, is distinct from the enablement requirement, which is acknowledged by the Examiner. However, the Examiner maintains that a description of a method of using a product must describe the product being used in order to meet the written description requirement. The claims recite a single process step (i.e., administering to the subject...). Applicant seems to be arguing that the invention is adequately described, even if the importation

competent signal peptide is not, because the specification describes the act of administering. However, it is the structure of the importation competent signal peptide itself, not administering, that dictates importation of the biologically active molecule. Surely it cannot be the case that a description of a method of delivering a bioactive molecule into a cell need not describe that which actually delivers the bioactive molecule into a cell. Applicant then goes on to reiterate the argument that a description of a process "need only describe the act to be performed" (page 13). These arguments are addressed herein above.

Finally, Applicant asserts that identification of additional importation competent signal peptides does not implicate the requirements of written description. Applicant argues, "the claim requires that the peptide, polypeptide, or protein be imported into the cell of the subject. This is an effect of the method, not a step of the method. Obtaining this effect is solely an issue of enablement, not written description. The effect is not a step or act required to perform the method, it is only a result that those of skill in the art must be able to obtain" (page 14). However, it is the Examiner's position that the step or act of administering is not fully described without a description of what is being administered. The claim is directed to a method of importing a biologically active molecule into a cell in a subject. Applicant is arguing that a description of the act of administering adequately describes this method even though the act itself is generic to all methods of treatment and, in and of itself, does not generally result in importation of a biologically active molecule into a cell. It is unclear how merely describing an action that does not result in a biologically active molecule being imported into a cell fully describes a method of importing a biologically active molecule into a cell. Applicant further argues, "how to make the importation competent signal peptides is at most only an aspect of how

to 'make' the claimed method because the materials to be used in a method are arguably part of 'making' such a method. Making the materials used in a claimed method is clearly not the method itself or a step in the method" (page 15). This argument is not found persuasive because the basis for the written description rejection is that the specification does not describe the importation competent signal peptide of the claims (the "how to make" requirement has been addressed in previous Office Actions and herein above with regard to enablement under 35 U.S.C. §112, first paragraph). For reasons also provided in previous Office Actions and herein above, the claimed method of using an importation competent signal peptide as a whole is not adequately described in the absence of a description of the importation competent signal peptide itself. Thus, Applicants arguments, when considered individually and as a whole, are not found persuasive and the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description for the claimed subject matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER